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Syndrome of Multiple Epiphyseal Dysplasia (Ribbing Type) With Rhizomelic Shortness, Cleft Palate, and Micrognathia in Two Unrelated Patients

R. Brian Lowry, Richard L. Wesenberg, and Judith G. Hall

Department of Medical Genetics, University of Calgary, and Alberta Children's Hospital, Calgary, Alberta, Canada (R.B.L.); Department of Diagnostic Imaging, Alberta Children's Hospital, Calgary, Alberta, Canada, and Department of Radiology, University of South Alabama, Mobile, Alabama (R.L.W.); Department of Pediatrics, University of British Columbia, and B.C.'s Children's Hospital, Vancouver, B.C., Canada (J.G.H.)

We report on two unrelated patietns with an apparently new syndrome. In each family they are the only affected members, their parents are not consanguineous, and paternal and maternal ages are not advanced.

At birth each patient was noted to have a marked Robin phenotype (cleft of the secondary palate and micrognathia) plus rhizomelic shortness. Delay in the appearance of long bone epiphyses was noted and followed by small fragmented and later very flat epiphyses of all long bones. The fibulae are short and radial heads dislocated. Scoliosis and marked genu valgum developed in both. Both patients have normal intelligence, vision, and hearing. Both have mildly upward slanting palpebral fissures, broad nasal tip, and apparent hypertelorism.

KEY WORDS: epiphyseal dysplasia, ribbing, cleft palate, micrognathia, dysmorphic facies, Robin sequence, diastrophic variant, Stickler syndrome

INTRODUCTION

Multiple epiphyseal dysplasia occurs as an isolated entity as exemplified by the Fairbanks and Ribbing types which are separate autosomal dominant traits. In these conditions the vertebrae are either normal or ony minimally involved which clearly separates them from the spondyloepiphyseal dysplasias. Epiphyseal dysplasia can also occur in a number of syndromes [Rimoin and Lachman, 1990; Spranger, 1976]. We report two patients whose spiphyseal dysplasia is very similar to the Ribbing type but who have other signs suggestive of a specific and different entity.

REPORTS

Patient 1 is the eldest of three daughters who were born to healthy non-consanguineous parents. They were both 21 years old at the time of the proposita's birth. The father is of English origin while the mother is German and Scottish. Both parents are 177 cm tall.

There was a small amount of vaginal bleeding in the first 3 months which did not require any therapy nor admission to hospital. The mother took Bendectin for nausea in the first trimester and two courses of antibiotics at 7 months for urinary tract infections. Labor and delivery were normal. The pregnancy lasted 33 weeks and the proposita weighed 1,830 g, i.e., she was born with intrauterine growth retardation, micrognathia, cleft palate, and short limbs particularly in the proximal segments. Birth length 45.5 cm. She was on a ventilator for 6 weeks due to repsiratory difficulties complicated by hyaline membrane disease. Her cleft aplate was an incomplete cleft of the secondary palate and was V-shaped rather than the usual broad U-shape in the Robin sequence. A skeletal survey showed shortness of the humeri and femora with flare of the ends. A diagnosis of Weissenbacher-Zweymüller syndrome was considered although she did not have a particularly flat face.

She had a palate repair at 11 months and at 1 year her height was 66 cm (<3 centile) and arm span was 59.5 cm. The proximal part of her arms and legs still looked short and she still had micrognathia.

Follow-up at $3^{11}/_{12}$ years disclosed that her height was now on the third centile (94.4 cm); her span was still markedly below her height (83.7 cm). Upper segment/lower segment ratio was 1.27, OFC was 51.4 cm (75th centile), and weight was 14.5 kg (10th–25th centiles).

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Address reprint requests to Dr. R.B. Lowry, Department of Medical Genetics, Alberta Children's Hospital, 1820 Richmond Road S.W., Calgary, Alberta T2T 5C7, Canada.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

There were some changes in the phenotype with presence of synophrys, a broad nasal tip, mild genu valgum, and mild pectus excavatum. She walked on her toes but her deep tendon reflexes were normal; there was no evidence of spasticity, and she had normal heel cords. A skeletal survey at 4 years showed definite flatness and irregularities of all epiphyses, particularly marked in the capital femoral epiphyses. Because of the possibility of Stickler syndrome she was examined by a pediatric ophthalmologist and her eyes were reported to be completely normal.

Over the next few years her genu valgum worsened but her height increased so that it was now between the 10th–25th centiles, but she developed scoliosis. The epiphyseal changes were again most marked in her hips with the knees and ankles being quite mild. Her fibulae were hypoplastic and disproportionately short at the proximal end. Apart from scoliosis her spine showed no significant changes. Her elbows and shoulders had mildly flattened epiphyses. The carpal bones were smaller than normal with hypoplastic ossification centers and the ulnar and distal radial epiphyses were mildly small. There was mild generalized brachydactyly primarily involving the metacarpals. No significant epiphyseal changes were seen in the hands and the phalanges were fairly normal in length. Over the next few years she had intermittent hip and knee pains which were thought to be synovitis. The pain seemed to be worse in the spring than at other times of the year and also worse at night. At 10 years her height was 130 cm (just under the 25th centile), span was 119 cm, and upper segment/lower segment ratio was 1.0. Her lumbar scoliosis was quite marked and there was almost no internal rotation at the hips. Genu valgum was more obvious. The following year she was put in a Boston brace but this did not prevent further progression and at age 14 years she had operative intervention by Zielke anterior spinal instrumentation with fusion of L1–L5. Her menarche occurred at age 14 years. At 16$^{9}/_{12}$ years her height was 154 cm (5th–10th centile), span was 138 cm, and upper segment/lower segment ratio was 0.95. Radiographs confirmed that her epiphyses were almost completely closed and flatter than normal with the capital femoral epiphyses being the most severely affected. There were also very short femoral necks. The joint space in both hips was satisfactory. Bony swelling of the proximal interphalangeal (PIP) joints were noted. She did not have generalized articular hypermobility and the range of movement in the upper limb joints was normal with the exception of the elbows which had reduced pronation and about 10° loss of complete extension. Both hips had limitation of movement with 30° loss of external rotation and flexion to 90°. The left knee hyperextended 10°. A rheumatology consultant did not consider her joint pains to be any form of an inflammatory process.

She is of normal intelligence and a very well-adjusted girl. Her physical findings are summarized in Table I and displayed in Figures 1–7.

Metacarpophalangeal pattern profile (MCPPP) at age 12 showed minimal shortness which was most

TABLE I. Physical Findings on Two Patients

	Patient 1	Patient 2
Epiphyseal dysplasia	+	+
Micrognathia	+	+
Cleft palate	+	+
Height centile	10	<5
Weight centile	25	<5
Head circumference centile	75	50
Rhizomelic shortness	+	+
Broad nasal tip	+	+
Palpeb fissure upslant	+	+
Scoliosis	+	+
Sternal abnormality	+	+
Brachydactyly	+	+
Short fibulae	+	+
Dislocated radii	+	+

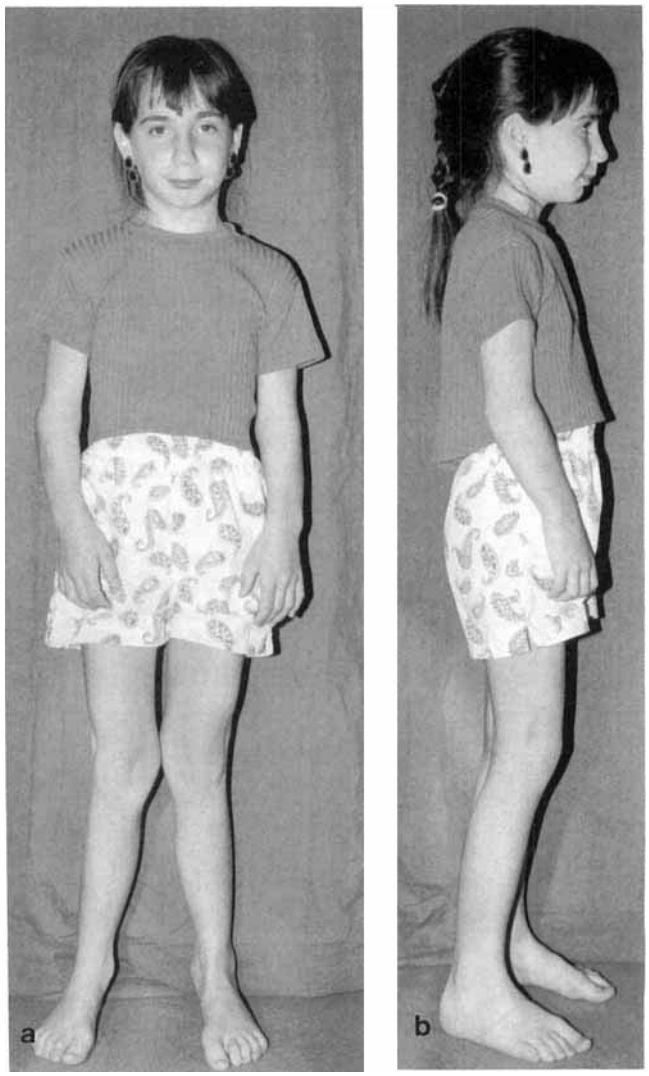

Fig. 1. Patient 1: 10 years. **a:** AP, note short upper limbs, genu valgum, prominence of right radial head. **b:** Lateral, showing micrognathia, slightly flexed elbows and knees.

Fig. 2. Patient 1: age 8 years, showing long nose with increased alar width, mild upward slanting palpebral fissures, and a trace of synophrys.

marked in the 2nd–5th metacarpals and in the 2nd middle phalanx with relative sparing of the distal phalanges and the proximal phalanges. She had a very symmetrical pattern which was not diagnostic of any syndrome.

Patient 2 is the third-born child of healthy non-consanguineous parents. He has an older sister and brother who are unaffected as are his parents. His father is of Scots-English origin and is 185 cm tall and his mother English and 165 cm tall. At the time of his birth their age was 29 and 28 years, respectively. The pregnancy lasted 38 weeks and birth weight was 2.95 g. At birth a diagnosis of Pierre Robin "syndrome" was made because of his cleft palate and micrognathia and also his choking spells which required suturing of his tongue. He was noted to have short arms and legs, a relatively long trunk, left talipes equino varus, and a right metatarsus adductus. His foot deformities were initially treated by casts but his left foot required multiple surgeries. He developed a marked genu valgum for which he had osteotomies at ages 10 and 11 years.

Fig. 3. Patient 1: 7⁹⁄₁₂ years AP radiograph of pelvis. Irregularity and flatness of femoral capital epiphyses and short femoral necks. Increased width of hip joint spaces. Hyperplastic, protuberant greater trochanters. Mild coxa vara deformity.

Fig. 4. Patient 1: age 7⁹⁄₁₂ years. AP radiograph of left arm and forearm. Subluxation of radial head, hypoplastic distal epiphysis of radius and ulna, increased carrying angle at elbow.

Because of his short stature and poor weight he was investigated at another center and a normal growth hormone response was present. Despite a normal endocrine work-up he was placed on an androgenic steroid from age 9¾ years to 11½ years with no apparent side effects. He gained 14.3 cm in height and 6.4 kg in weight. A heart murmur interpreted as a functional murmur. At 9 years an ophthalmologist reported that his visual acuity was normal and there were no eye abnormalities.

He was first seen in the Genetics clinic when he was 11¹¹⁄₁₂ years old. At that time his height was 136.6 cm (5th centile), weight was 27.7 kg (<5th centile), and head circumference was 53.6 cm (50th centile). Span was 126 cm, upper segment/lower segment ratio was 1.08, inner and outer canthal distances were 3.2 and 8.7 cm (60th centile), and interpupillary distance was 5.7 cm (75th centile). Apart from eccentrically placed pupils his eyes were normal and this was confirmed by a pediatric ophthalmologist. The latter reported that he

Fig. 5. Patient 1: age 7$^{9}/_{12}$ years. PA radiograph of hands. Flat epiphyses, most marked in the metacarpals and distal epiphyses of radius and ulna. Tapering and absent ossification of distal radial epiphyses medially. Tapering and deficient ossification of distal ulnar epiphyses laterally. Widened, slightly bulbous distal ends of proximal phalanges, contributing to clinical impression of swollen PIP joints. Mild proximal flare of middle phalanges of digits II–V is evident. There is premature closure of physes of all distal and middle phalanges. Narrowing of all DIP and PIP joints is noted. Mildly dysplastic irregularities of contour of all carpal bones are noted. There is deficient ossification of the navicular bones proximally. Brachymetacarpalia of metacarpals II–V has resulted in nearly equal lengths of metacarpals.

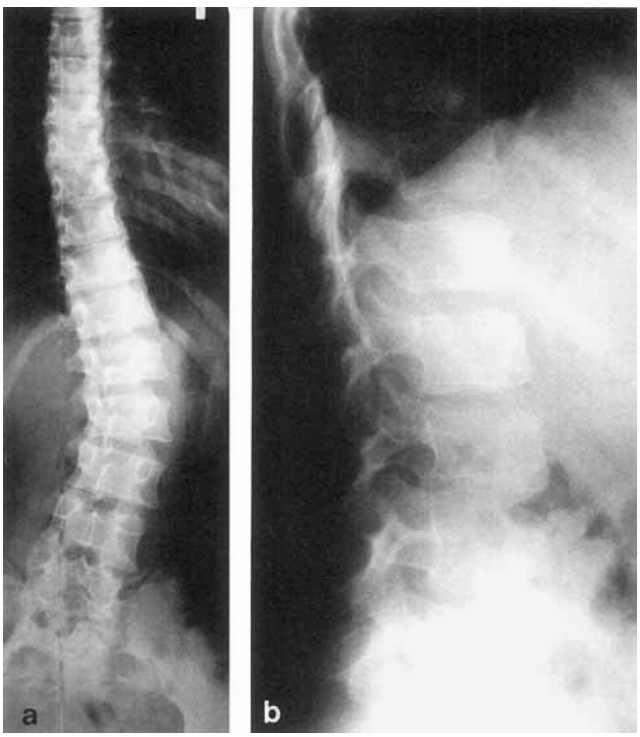

Fig. 6. **a:** Patient 1: age 9$^{9}/_{12}$ years. AP dorsolumbar spine film. Dorsolumbar levoscoliosis with normal vertebral body height. **b:** Lateral lumbar spine radiograph. Age 7$^{9}/_{12}$ years: normal vertebral height. Mild anterior "humping" of superior and inferior vertebral body end plates of lower dorsal and upper lumbar vertebrae.

Fig. 7. Patient 1: age 7$^{9}/_{12}$ years. AP radiograph of legs. Genu valgum, mildly flat epiphyses, and short proximal end of fibulae. Mild notch in medial proximal tibila epiphyses bilaterally. Mild tibial diaphyseal bowing. Distal tibial epiphyses taper laterally resulting in mild talar tilt.

did have some tortuosity of vessels but did not consider it to be markedly abnormal.

The patient had a broad nasal tip with an apparently long philtrum although measurements actually placed this in the 50th centile, and mild retrognathia. Both ears were apparently low-set, small, and had a posterior slant (35°). Their size was 5.2 and 5.3 cm (10th centile). He had a high arched palate with many horizontal ridges, but there was good mobility of the previously repaired soft palate.

He had restricted range of movement in many joints as follows: elbows had incomplete extension, about 20° left and 15° right, incomplete pronation and supination, shoulders only abducted to 90·, and there was almost no dorsiflexion of his writsts. His hands had very short fingers with borad PIP joints. His thumbs appeared proximally placed with poor thenar musculature and the left thumb was more pointed distally with a smaller nail than the right thumb. There was no camptodactyly or syndactyly but the left index finger deivated mildly in an ulnar direction. Right palm was at 9 cm (25th centile) and mid finger was 6.2 cm (3rd

centile). He had a mild dorsal scoliosis and prominent kyphosis. In the lower limbs tehre was some limtation of internal and exteernal rotation of the hips but he had normal abduction and flexion. There was marked genu valgum, a rigid left ankle joint due to surgery for his left TEV, and the muscles of his left calf were hypoplastic. Other findings included marked pectus carinatum, a functional cardiac murmur and normal pubertal development (Tanner stage 3). His intelligence is normal.

Radiographs showed generalized osteopenia with irregularity and fragmentation of the epiphyses. He had bilateral radial head dislocation, mild scoliosis, and mild platyspondyly of cervical vertebrae 6 and 7 with ring epiphyseal abnormalities but the rest of his vertebrae showed no platyspondyly. The carpal bones were irregular and there was coning of his digital epiphyses.

Follow-up examination at age 18 years showed that he wa sin good general health, visual acuity was normal, and repeat ophthalmologic examination confirmed that his eyes were normal. His hearing is normal and he was in grade 12. He sometimes had pain in his hips and in his left knee and the major problem was that his scoliosis was progressing. His height at that time was 155 cm (<5th centile), span was 148 cm, upper segment/lower segment ratio was 1.17, and head circumference was 56.1 cm (50th centile). His interalar width was 3.8 cm (95th centile). There was limitation in most of his hip movements. His findings are illustrated in Figures 8–14.

Fig. 8. Patient 2: age 12 years. **a:** Note long nose with increased alar width, mild upward slanting palpebral fissures. **b:** Mild retrognathia, apparently low-set posteriorly angulated ear.

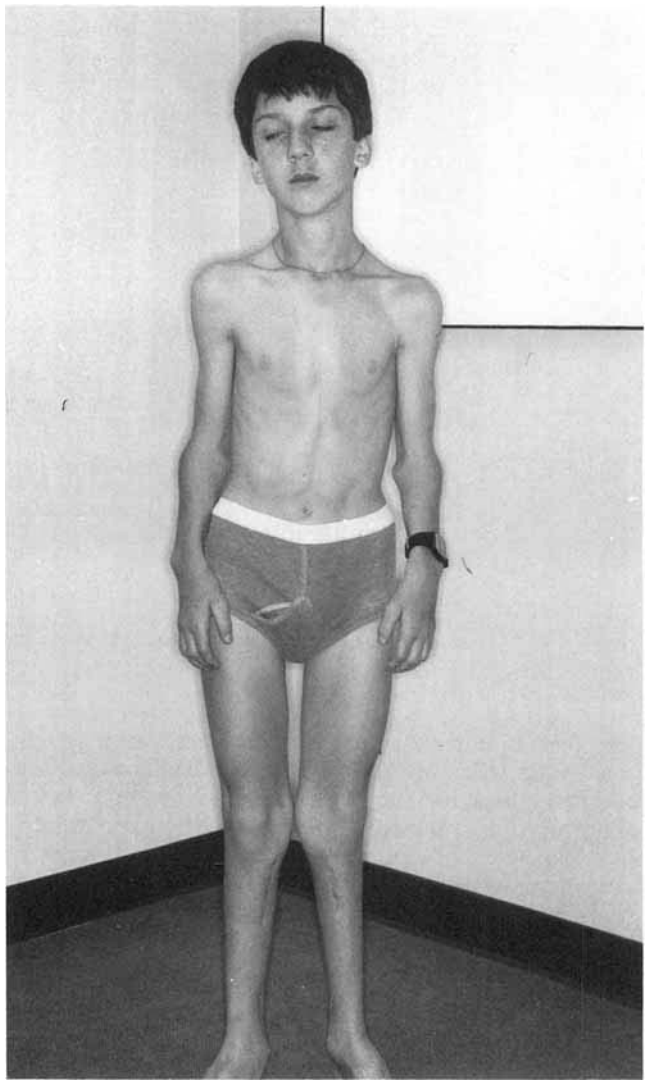

Fig. 9. Patient 2: age 12 years. Rhizomelic shortness with prominent radial heads, genu valgum, and pectus carinatum.

DISCUSSION

These two unrelated patients appear to have a very similar phenotype consisting of small flat epiphyses particularly in the capital femoral epiphyses, cleft of secondary palate, micrognathia at birth giving the appearance of Robin sequence, and rhizomelic shortness. They have a similarly broad nasal tip and mid nose, mildly upward slanting palpebral fissures, relative hy-

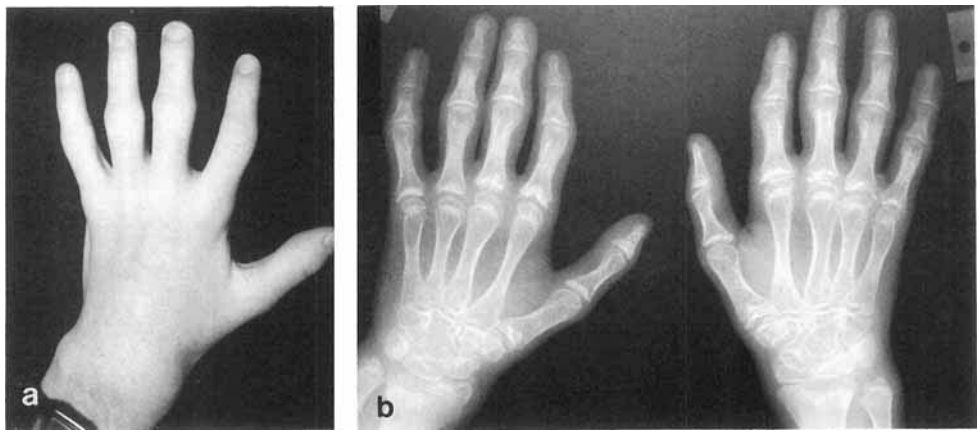

Fig. 10. **a:** Patient 2. Left hand: prominent proximal interphalangeal joints, pointed left thumb with small nail, and short digits. **b:** Age 11 7/12 years. PA radiograph of hands. Note numerous flattened and coned phalangeal epiphyses, hypoplastic distal radial and ulnar epiphyses, and nearly equal lengths of metacarpals II–V with diffusely flat epiphyses. There is prominent widening with a bulbous appearance of the distal ends of proximal phalanges II–V. There is proximal flare of the middle phalanges of all the digits with narrowing of PIP and DIP joints. Note premature closure of all phalangeal growth plates (physes). The bony changes simulate clinical findings in rheumatoid arthritis. Mildly dysplastic carpal bones are noted. The navicular bones are hypoplastic proximally. The distal radial epiphysis tapers and has lack of ossification medially and the ulnar epiphysis tapers laterally.

pertelorism, and mild joint contractures. Their stature is variable with patient 1's height initially <3rd centile but changing to the 10th–25th centile before declining to the 5th–10th centile probably due to scoliosis. Patient 2's height was <3rd centile but after the androgenic steroids had three successive values on the 5th centile but now at age 18 years his height is well below the 5th centile and again some of this loss is probably due to this progressive scoliosis and short femoral necks. Both have sternal abnormalities, short fibulae, genu valgum, and brachydactyly with widening at the PIP joints. Patient 2 has some localized platyspondyly of cervical vertebrae 6 and 7 and also cone epiphyses of the digits. Both have normal intelligence, vision, and hearing and do not have articular hypermobility.

A number of diagnoses were considered, particularly the Stickler syndrome but neither have any eye signs nor do they have the flat mid face. Their radiographic findigns are also against such a diagnosis [Taybi and Lachman, 1990]. Diastrophic variant is another consideration but their other findings probably preclude this diagnosis [Horton et al., 1978; Lachman et al., 1981].

We consider that they have a unique syndrome whose cause is unknown. Since most epiphyseal dysplasias are gene determined it seems likely that it is genetic but could be either an autosomal dominant or autosomal recessive trait.

Fig. 11. Patient 2: age 11 7/12 years. AP radiograph of pelvis. Very small, flat capital femoral epiphyses with incomplete ossification inferomedially and short femoral necks. Mild coxa vara deformity. Hyperplastic, protuberant greater trochanters. Mildly irregular acetabulae with small lateral notches bilaterally.

Fig. 12. Patient 2: age 11 7/12 years. PA radiograph of knees. Mildly flat dysplastic distal femoral and proximal tibila epiphyses. Lateral notching of the proximal tibial epiphyses is evident. The proximal end of the fibulae is short.

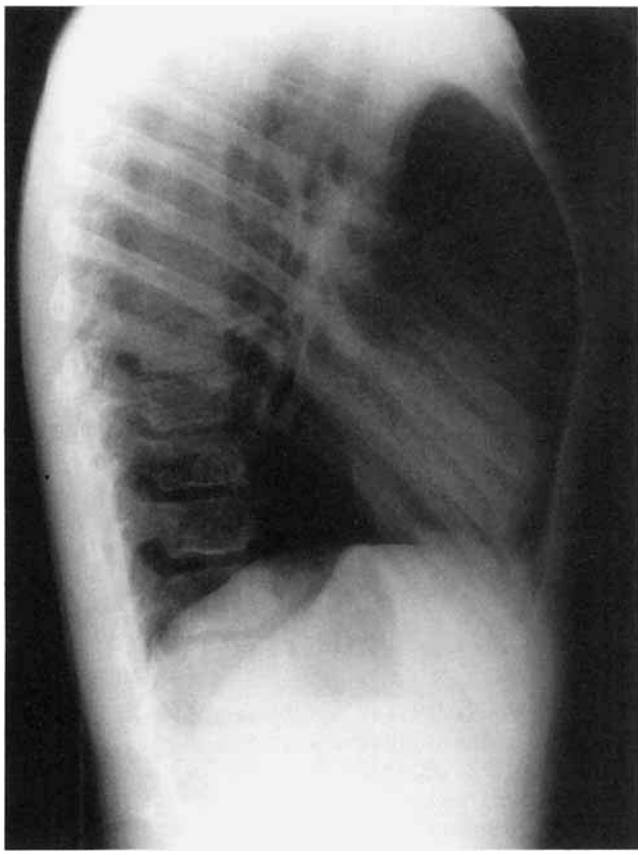

Fig. 13. Patient 2: age 11 7/12 years. Lateral dorsal spine radiograph. A mild upper dorsal kyphosis is present. There is mild anterior "humping" of the superior and infereior end plates of the lower dorsal and upper lumbar vertebrae. Scoliosis was present (not shown).

Fig. 14. Patient 2: age 11 7/12 years. AP radiograph of right elbow. Dysplastic proximal ulnar and radius with frankly dislocated radius (anterolaterally). Note flattened, thin, proximal radial epiphysis.

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ADDENDUM

These patients were presented as a poster presentation at the 8th International Congress of Human Genetics, 1992.

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